UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: 11/6/12

SUBJECT: **Iprodione.** Human Health Assessment Scoping Document in Support of Registration Review.

PC Code: 109801
Decision No.: 465586
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: N/A
MRID No.: N/A

DP Barcode: D402505
Registration No.: N/A
Regulatory Action: Registration Review
Case No.: 2335
CAS No.: 36734-19-7
40 CFR: §180.399

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Executive Summary

The Health Effects Division (HED) Iprodione Registration Review Team has evaluated the status of the human health risk assessment for iprodione to determine the scope of work necessary to support Registration Review. The most recently completed human health risk assessment conducted to support the Registration Eligibility Document (RED) published in November 1998

(D233218, C. Scheltema, 7/31/1998), as well as updated dietary (D392706, D. Davis, 3/15/12) and occupational and residential (D389181, M. Lloyd, 3/7/12) exposure and risk assessments were considered as part of this scoping exercise.

Based on the currently registered uses, exposures to iprodione can be expected to occur via the dietary (food and drinking water), occupational (handler and post-application), and residential (handler and post-application) exposure pathways for iprodione and through the oral, dermal, and inhalation routes of exposure.

Iprodione is a systemic fungicide used on a wide variety of agricultural crops, as well as on institutional turf, including sod farms, commercial lawns, golf courses, sports fields, etc. Iprodione shares a common metabolite, 3,5-dichloroaniline (3,5-DCA), with the active ingredients vinclozolin and procymidone. Therefore, risks need to be considered not only for parent and other regulated metabolites, but also for aggregate 3,5-DCA resulting from application of iprodione, procymidone and vinclozolin.

The toxicity data base for iprodione is incomplete, but is adequate for assessing risk with retention of the FQPA safety factor. A 2-generation reproduction study (870.3800) and an inhalation toxicity study (870.3465) are required for registration review. Once those data have been received and reviewed, their impact on the regulatory endpoints, points of departure (PoDs) and uncertainty factors/safety factors (UF/SFs) will need to be evaluated.

The residue chemistry database for iprodione is incomplete. An adequate enforcement method for livestock commodities is required and a residue decline study in rice water is required. The registrant was informed of both these deficiencies in the Registration Eligibility Decision Document (RED). The tolerance expression in the 40CFR should be updated to reflect current policy.

The Agency recently updated the drinking water assessment for iprodione and conducted highly refined acute, chronic and cancer dietary (food and water) risk assessments. No acute or chronic (non-cancer) dietary risks of concern were identified. Iprodione estimated cancer risk from drinking water alone is 1.7×10^{-5}. Iprodione estimated cancer risk from the currently registered food uses is 7.8×10^{-6}. The estimated 3,5-DCA cancer risk for water alone from the registered turf use is 3.9×10^{-5}. The estimated 3,5-DCA cancer risk from food (imported wine grapes only) is 5.6×10^{-7}. These dietary assessments reflect all available refinements and were conducted in compliance with current scientific policies and practices; therefore, a new assessment will be required only if new data are provided which impact the PoDs, UF/SFs, or drinking water residues used in this assessment.

The residential exposure database is complete. A revised residential exposure assessment may be required under registration review that includes post-application exposure to adults and children playing on commercially treated turf. This assessment should incorporate, as necessary, the additional toxicology studies that have been submitted to HED as well as the recently updated *Health Effects Division's 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment.*

An updated aggregate risk assessment may be required to support the registration review which incorporates any new PoDs, UF/SFs, any revisions to the drinking water assessment, as well as the findings from the updated non-occupational (residential) assessment.

The occupational exposure database is complete. Updated occupational handler exposure assessments may be required under registration review based upon revisions to the Agency's scenario-specific surrogate handler exposure data and updated commercial seed treatment methodology. An occupational post-application assessment may be required under registration review which incorporates recently received dislodgeable foliar residue (DFR) data.

Introduction

HED has evaluated the most recent complete human health risk assessment for iprodione conducted in 1998 in conjunction with the RED, as well as recently conducted dietary risk assessments, to determine if sufficient data are available and if updates are needed to support registration review. HED has also considered updates to its toxicity, exposure and usage databases, and the latest Agency science policy and risk assessment methodologies.

Iprodione is a contact and/or locally systemic fungicide registered for use on a variety of field, fruit, and vegetable crops in agricultural settings. Iprodione is currently registered for use on institutional turf, including sod farms, commercial lawns, golf courses, sports fields, etc. Iprodione is restricted from use on residential turf/lawns.

Information on the chemical identify of iprodione is included in Attachment 1.

Hazard Identification/Toxicology

The toxicity database for iprodione is incomplete but sufficient for assessing risk with retention of the FQPA safety factor.

Iprodione is associated with toxicity of the liver, adrenals, and male and female reproductive organs in animal studies. Iprodione has been shown to alter anogenital distances in male fetuses following exposure during late gestation, to delay male sexual maturation and decrease testosterone levels in immature male rats, and there is evidence of toxicity to the male reproductive organs in chronic studies in rats, as evidenced by increased interstitial cell hyperplasia, reduced epididymidal spermatozoa, and reduced secretion of the seminal vesicles. Reproductive function was not affected in the 2-generation reproduction study performed under the old protocol. The prenatal developmental toxicity study in rabbits, a special prenatal study in rats, and the two-generation reproduction study in rats showed no indication of increased susceptibility to *in utero* and/or postnatal exposure to iprodione. Iprodione does not pose a genotoxic hazard, but has been classified as a "Likely" human carcinogen based on an increased incidence of liver tumors in both sexes of the mouse and an increase incidence of Leydig cell tumors in male rats. The proposed mode of action (MOA) of iprodione for Leydig cell tumors is disruption of testosterone biosynthesis; however, sufficient information is not available to

delineate a definitive MOA for either tumor type; therefore, the Agency is regulating carcinogenicity using a linearized low dose extrapolation model (Q1* approach) based on the Leydig cell tumors. Iprodione does not appear to be a frankly neurotoxic chemical. There is no concern for immunotoxicity.

The iprodione metabolite, 3,5-DCA, is assumed to pose a potential cancer hazard based on its structural similarity to para-chloroaniline (PCA). 3,5-DCA is a common metabolite of iprodione, vinclozolin, and procymidone; therefore, a separate aggregate cancer risk assessment considering this metabolite is required. The established Q_1* of 6.38 x 10^{-2} $(mg/kg/day)^{-1}$ for PCA was used in this assessment as the Agency believes that the use of the PCA Q_1* represents a reasonable upper bound risk estimate.

Acute and subchronic neurotoxicity studies in rats, which are required in accordance with new data requirements for conventional pesticide registration (40 CFR Part 158), have not been submitted. However, based on a weight-of-evidence (WOE) approach, considering all the available iprodione hazard and exposure information, the HED Hazard and Science Policy Council (HASPOC) concluded that the acute and subchronic neurotoxicity studies are not required for iprodione at this time (TXR No. 0056453, 10/16/12). Based on current policies, a repeat dose inhalation toxicity study in rats is required due to the potential for repeated inhalation exposure to aerosolized formulations of iprodione. The HASPOC determined that a 28-day inhalation toxicity study is required for iprodione to better estimate risk for occupational inhalation exposure.

Previously, HED concluded that an assessment of effects on the male reproductive system following pre- and/or postnatal exposure was required, and these aspects could be assessed by conducting a 2-generation reproduction study, as described in OCSPP 870.3800. However, these data were never formally requested. These data are still necessary to fully characterize iprodione hazard and should be required.

The most recent dietary risk assessment for iprodione was conducted in 2012 (D392706, D. Davis, 3/15/12) and included review of the available toxicity data for iprodione, consideration of current policies, and a re-evaluation of endpoints for risk assessment. New acute and chronic toxicological points of departure (PODs) were selected for dietary risk assessment, and new endpoints were selected for occupational and non-occupational short and intermediate term dermal and inhalation exposure scenarios. The toxicity profile tables for iprodione are included as Attachment 2. The iprodione endpoints, points of departure (PoDs), and uncertainty/safety factors (UF/SFs) are summarized in Attachment 3.

The most sensitive endpoint in the iprodione database is the reduction of testosterone. The point of departure (POD) used for all exposure risk assessments was selected from a male rat pubertal assay, based on reduced serum levels of testosterone. An uncertainty factor of 1000X was applied to the endpoint selected for all routes and durations of exposure (10X for interspecies extrapolation, 10X for intraspecies variation, 10X FQPA SF). The FQPA safety factor accounts for the lack of a NOAEL in the testosterone data ($UF_{LOAEL \rightarrow NOAEL}$) and for the lack of the guideline studies (reproduction study, 870.3800 and 28-day inhalation toxicity study, 870.3465). Since testosterone is the basis of the acute and chronic risk assessments and is considered the

endpoint that is protective of all other downstream effects in males or females and further, since testosterone levels would be affected before, and at a dose level equal to or lower than, any other potential effects that may occur following repeat exposure, there are no residual concerns.

Conclusions

The following toxicity studies are required for registration review: a 2-generation reproduction study (870.3800) and an inhalation toxicity study (870.3465). For both studies, serum testosterone measurements should be included. A protocol for each study should be provided to the Agency for review prior to undertaking the studies. These two studies have not been previously formally requested of the registrant and should be called-in in connection with registration review. Once these studies have been received and reviewed, the impact of this data on the endpoints for regulation, PoDs, and UFs will need to be reevaluated.

Dietary Exposure

The residue chemistry database for iprodione is incomplete. An adequate enforcement method for livestock commodities and data on residue decline in rice water have not been provided.

The nature of the residue in plants and animals is adequately understood. The residues of concern for both tolerance setting and risk assessment purposes in plants are iprodione, its RP-30228 isomer, and its RP-32490 metabolite. The residues of concern for both tolerance setting and risk assessment purposes in livestock are iprodione, its RP-30228 isomer, and metabolites RP-25040 and RP-44227. Additionally, the iprodione 3,5-DCA metabolite, which is also a common metabolite of vinclozolin and procymidone, poses a potential cancer concern and a separate risk assessment is required for this metabolite. The residue of concern in rotational crops is not adequately understood at this time. However, currently, iprodione labels limit rotation only to those crops for which there is a primary use; therefore no additional data are required with respect to rotational crops.

An adequate analytical method for enforcing tolerance in plant matrices is available. The HED Chapter of the RED for Iprodione (D233218, C. Scheltema, 7/31/1998) noted that an adequate method for the detection of all the regulated residues in livestock was not available. The registrant, Bayer CropScience, formerly Aventis CropScience, met with the Agency on February 8, 2000 to present a new method for the determination of residues in livestock commodities. The Agency recommended that the registrant submit the method, along with an independent method validation (ILV) for Agency review (D262487, W. Smith, 6/7/2000). There is no record that the method was ever submitted for Agency review. Requirements for multi-residue method testing have been satisfied for iprodione.

Field trial data generated using acceptable data collection methods and supported by adequate storage stability data are available for all registered crops. Adequate processing studies are available. Adequate livestock feeding studies have been submitted for iprodione.

The RED indicated that a decline study in rice water was required and that the registrant committed to conduct a study. No record is available to indicate that these data were received and reviewed. Therefore, this data remain an outstanding data gap.

A drinking water assessment (D359480, C. Peck, 2012) was conducted by the Environmental Fate and Effects Division which modeled separately the estimated drinking water concentrations (EDWCs) for iprodione residues of concern (iprodione and the three degradates RP30228, RP35606, and RP 32490) and 3,5-DCA in surface water and groundwater. 3,5-DCA was assessed separately because the toxicity endpoint for 3,5-DCA is different from that of iprodione. EFED has concluded that pending receipt and review of additional environmental fate and toxicity data for iprodione and its degradates, or changes in labeled use rates, the drinking water assessment will be reevaluated. However, if no new, relevant data regarding the environmental fate, toxicity, or use of iprodione or its degradates are submitted, the EDWCs from the 2012 drinking water assessment will be used in the registration review risk assessment.

The Agency conducted highly refined acute probabilistic, chronic, and cancer risk assessments for iprodione and its regulated metabolites and a separate cancer dietary risk assessment for 3,5-DCA from iprodione, vinclozolin and procymidone. Refinements to the dietary assessment included the use of monitoring data, percent crop treated information, empirical processing factors, and modeled drinking water values. Iprodione acute and chronic (non-cancer) dietary (food and water) risks were not of concern. Iprodione estimated cancer risk from drinking water alone is 1.7×10^{-5}. Iprodione estimated cancer risk from the currently registered food uses is 7.8×10^{-6}. The estimated 3,5-DCA cancer risk for water alone from the registered turf use is 3.9×10^{-5}. The estimated 3,5-DCA cancer risk from food (imported wine grapes only) is 5.6×10^{-7}.

Conclusions

The residue chemistry database is incomplete. A livestock enforcement method and submission of a residue decline study in rice water are required. These data have been previously requested. All other residue chemistry data requirements have been adequately addressed.

Should the required toxicology data impact the PoDs or UF/SFs for risk assessment, or should the registrant provide additional data which may be used to refine the drinking water assessment, the Agency may need to update the dietary risk assessment for iprodione and 3,5-DCA. In the absence of new information; the referenced assessment reflects all available refinements and current science policy and practices and would not need to be updated for registration review.

Residential Exposure and Risk

As noted above, iprodione is currently registered for use on institutional turf, including sod farms, commercial lawns, golf courses, sports fields, etc. Iprodione is restricted from use on residential turf/lawns. Based on these uses, adults and children may experience exposure to iprodione as a result of contacting commercially treated turf (i.e., residential post-application exposure).

In accordance with the updated Part 158 data requirements (2007), a turf transferable residue (TTR) study is required for all occupational (e.g., sod farms, golf courses, parks, and recreational areas) or residential turf uses, and that TTR data are available for iprodione.

The 1998 RED addressed mitigations involving residential exposure. Specifically, the RED addressed cancelling residential uses of iprodione on small gardens, home ornamentals, and the residential uses of iprodione on turf. Since the 1998 RED, additional toxicology studies have been submitted to HED, registered use sites have changed, and the *Health Effects Division's 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment* have recently been updated. A March 2012 assessment (D389181) for proposed new agricultural uses of iprodione partially reassessed aggregate exposure and risk. Specifically, the assessment evaluated iprodione dermal post-application exposure (cancer and non-cancer) for casual golfers using the updated iprodione PoDs and UF/SFs, the 2012 SOPs, and available turf transferable residue (TTR) data. Non-cancer post-application dermal golfer risk estimates are not of concern. Post-application cancer risk estimates range from $3.2x10^{-6}$ to $1.8x10^{-5}$.

Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for iprodione. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices, and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website[1]. On a chemical-by-chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT® computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray-drift-management practices to reduce off-target drift with specific products with significant risks associated with drift.

Conclusions

The residential exposure database is adequate to support the registration review process for iprodione. A revised residential exposure assessment (cancer and non-cancer) may be required under registration review that includes post-application exposure to adults and children playing on commercially treated turf. This assessment should incorporate, as necessary, the additional toxicology studies that have been submitted to HED, updated human factors (e.g., body weight) assumptions, and the 2012 Revised Residential SOPs.

Aggregate Risk Assessment

The most recently completed aggregate risk assessment was conducted in connection with the 1998 RED. As indicated above, additional toxicity data is required which may impact the PoDs and UF/SFs for use in risk assessment. Additionally, an updated non-occupational (residential) assessment may be required. Lastly it is possible that additional data may be provided with

[1] Available: http://www.epa.gov/opp00001/factsheets/spraydrift.htm

which to update the drinking water assessment. Consequently, a revised aggregate risk assessment for iprodione may be required for registration review.

Occupational Exposure

As noted above, iprodione is registered for use on a variety of field, fruit, and vegetable crops, including almonds, grapes, peaches, potatoes, rice, berries, onions, peanuts, lettuce, and is also registered for use on golf courses, commercial turf, and ornamentals. The Agency has determined that there is a potential for occupational handler and post-application exposures resulting from the registered uses of iprodione.

Occupational Handlers

The 1998 RED evaluated a number of occupational handler scenarios that represented the major iprodione occupational handler scenarios based on application equipment and formulation type. That assessment indicated that occupational handler scenarios resulted in inhalation risk estimates of concern for some exposure scenarios (e.g., high acreage aerial/chemigation applications, belly grinder mix/load/apply applications). Risk mitigation measures mentioned in the RED included additional personal protective equipment for a number of occupational handler scenarios. Additionally, the RED indicated data gaps for iprodione handler commercial seed treatment exposure scenarios. Since the RED, HED has reevaluated the hazard database for iprodione, there have been changes to the registered use pattern, and there is new unit exposure data available to assess occupational handler scenarios. Because of these changes, HED will likely reevaluate the occupational handler assessment for iprodione.

Occupational Post-application

The 1998 RED addressed occupational post-application exposures with default dislodgeable foliar residue (DFR) data. Based on this assessment, the restricted-entry interval was set to 48-hours for use of iprodione on grapes and ornamentals, and to 24-hours for all other iprodione uses. Technical iprodione is currently classified as toxicity category III/IV for acute dermal toxicity, primary eye, and skin irritation.

In accordance with the updated Part 158 data requirements (2007), one or more DFR studies are required when a pesticide has residential or occupational uses that could result in post-application dermal exposure. Since the RED, three DFR studies (on lettuce, peaches, and grapes) have been submitted for iprodione. Review of the lettuce DFR study is complete and review of the peach and grape study is under way. Screening assessments of the primary DFR studies indicate that they are suitable for use in human health risk assessment.

Conclusions for Occupational Exposure and Risks

The occupational exposure database is complete. Updated occupational handler exposure assessments may be required under registration review based upon revisions to the Agency's scenario-specific surrogate handler exposure data[2] and exposure methodology relating to commercial seed treatment. Additionally, an updated occupational seed treatment assessment and occupational post-application assessment (cancer and non-cancer) for foliar applications of

[2] - Available: http://www.epa.gov/pesticides/science/handler-exposure-table.pdf

iprodione to agricultural crops (using the newly available DFR study data) may be required under registration review.

Public Health and Pesticide Epidemiology Data

The Agency has reviewed the available incident data for iprodione (D404146, S. Recore, 7/31/12) and concludes that based on the low frequency and severity of incident cases reported for iprodione, there does not appear to be a concern at this time that would warrant further investigation. The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be included in the risk assessment.

Tolerance Assessment and International Harmonization

Tolerances for iprodione are established under 40 CFR §180.399 for the combined residues of iprodione, its isomer RP30228 (3-1-methylethyl)-*N*-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine-carboxamide) and its metabolite RP32490 (3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine-carboxamide) in/on a variety of plant commodities. Tolerances for livestock commodities are established for the combined residues of iprodione, its isomer RP30228, and its metabolites RP32490 and RP36114 ([*N*-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide]).

According to HED's Interim Guidance on Tolerance Expressions (5/27/09, S. Knizner), the tolerance expression for iprodione on plant commodities should be revised to state:

> "Tolerances are established for residues of iprodione, including its metabolites and degradates, in or on the commodities in the tables below. Compliance with the tolerance levels specified below is to be determined by measuring the sum of iprodione [3-(3,5-dichlorophenyl)- *N* -(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide], its RP-30228 isomer [3-(1-methylethyl)- *N* -(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide], and its RP-32490 metabolite [3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine-carboxamide].

The appropriate tolerance expression for livestock will be determined when an acceptable enforcement method has been submitted.

At this time, there are no pending requests for the establishment of new tolerance for iprodione.

The International Residue Limit Status Sheet is attached to this document as Attachment 4.

There are no Codex, Canadian, or Mexican Maximum Residue Limits (MRLs) established for livestock commodities; therefore a discussion of harmonization of livestock tolerance expression or levels is not required for this active ingredient. There are no Mexican MRLs for iprodione on plant commodities. The U.S. plant residue definition is harmonized with Canada, but is not harmonized with Codex. Both the U.S. and Canada include the iprodione isomer and a metabolite in their tolerance expression, while Codex regulates on parent only. Despite the residue definition discrepancy, levels are harmonized between Codex and the U.S. on several

commodities including succulent beans, broccoli, leaf lettuce, and rice grain. However, because of the inclusion of only the parent in Codex MRLs, it may not be possible to harmonize with Codex values that are lower than the current U.S. tolerances since the Codex MRL may not be adequate to cover the regulated residues in the U.S. (almonds, dry beans, cherries, grapes, kiwifruit, head lettuce, bulb onions, peaches, and strawberry). For those commodities where Codex has established a higher tolerance, despite the residue definition discrepancy, it is possible that levels can be harmonized (caneberries, and carrots). U.S. tolerances and Canadian MRLs are harmonized for carrots only. For most commodities Canadian MRLs are significantly lower than the U.S. tolerances (apricot - 20 ppm vs. 3 ppm, dry bean - 2 ppm vs. 0.3 ppm, caneberries – 25 ppm vs. 10 ppm for Canadian raspberries, cherries – 20 ppm vs. 5 ppm, grape – 60 ppm vs. 10 ppm, raisins 300 ppm vs. 60 ppm, kiwifruit – 10 ppm vs. 0.5 ppm, lettuce 25 ppm vs. 15 ppm, nectarine – 20 ppm vs. 10 ppm, peach 20 ppm vs. 10 ppm, plum 20 ppm vs. 2 ppm, prune 20 ppm vs. 2 ppm, and raspberry 15 ppm vs. 10 ppm) suggesting that the current Canadian MRL levels would not be sufficient to cover residues resulting from the U.S. use patterns.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in the human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/nepa/tools/guidance/Volume1/2-6-EO_12898envjustice.pdf). The Office of Pesticide Programs (OPP) typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who may be exposed when harvesting crops. Should these highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

Cumulative

EPA has not, at this time, made a determination as to whether iprodione shares a common mechanism of toxicity with any other substances.

Human Studies

The previous iprodione risk assessments relied in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. Studies such as the Pesticide Handlers Exposure Database, Outdoor Residential Exposure Task Force, and Agricultural Handler Exposure Task Force have been reviewed by the Agency and found on the basis of available evidence to have been neither fundamentally unethical nor significantly deficient relative to standards of ethical research conduct prevailing when they were conducted. There is no barrier in EPA's "Protection of Human Subjects" Regulation to reliance on these studies.

Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), iprodione is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. Iprodione was included on that list and has been issued an order to conduct the Tier 1 testing. Once all required Tier 1 and Tier 2 data have been received and reviewed, the endpoints and safety factors used for risk assessment purposes will be examined and a new risk assessment performed if necessary. For further information on the status of the EDSP, the policies and

procedures, the list of 67 chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

Data Requirements

The following toxicity studies are required to support the registration review of iprodione:

- 2-generation reproduction study (870.3800)
- inhalation toxicity study (870.3465)

For both studies, serum testosterone measurements should be included. A protocol for each study should be provided to the Agency for review prior to undertaking the studies.

The following residue chemistry data are required to support the registration review of iprodione:

- An analytical enforcement method for livestock
- Residue decline in rice water

References

Table 1: HED Memoranda Relevant to Registration Review

Author	Barcode/TXR #	Date	Title
C. Scheltema	D233218	07/31/1998	The HED Chapter of the Reregistration Eligibility Decision Document (RED) for Iprodione (PC Code: 109801, List A Case No. 2335, DP Barcode: D233218).
D. Davis	D392706	3/15/12	**Iprodione**. Acute Probabilistic, Chronic and Cancer Aggregate (Food and Drinking Water) Dietary Exposure and Risk Assessments for Parent and 3,5-DCA to Support New Section 3 Registration Actions on Cucurbits (Crop Group 9) and Fruiting Vegetables (Crop Group 8-10)and to Support a Tolerance for Imported Canola.
K. Rury	TXR# 0056453	10/16/12	**IPRODIONE:** Summary of Hazard and Science Policy Council (HASPOC) Meetings: Recommendations on the need for the inhalation, and acute and subchronic neurotoxicity studies.
S. Recore	D404146	08/01/2012	Iprodione: Review of Human Incidents

Table 1: HED Memoranda Relevant to Registration Review			
Author	**Barcode/TXR #**	**Date**	**Title**
T. Goodlow	D381906	12/15/2010	Iprodione: Proposed Label Amendment for Use on Peanuts.
T. Dole	D338091	01/04/2008	Occupational Risk Assessment for the Proposed Deletion of the Water Soluble Bag Requirement for Wettable Powder Formulations of Iprodione Applied Via Chemigation to Ornamentals
M. Lloyd	D389181	03/07/2012	Iprodione: Occupational Exposure and Risk Assessment for the Proposed New Uses on Cucurbits, Fruiting Vegetables (includes Updated Non-Occupational Cancer Assessment).

Attachments

Attachment 1. Chemical Identity
Attachment 2. Toxicity Profile Tables
Attachment 3. Endpoint Tables
Attachment 4. Iprodione International Residue Limits Table

Attachment 1. Iprodione Chemical Identity

Table A1.1. Iprodione Nomenclature.

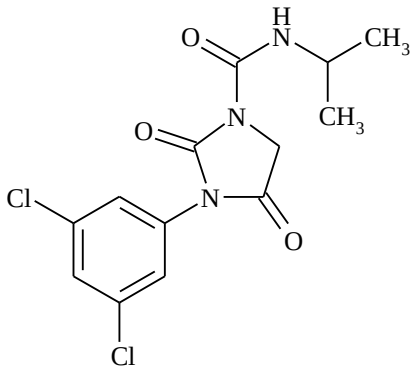
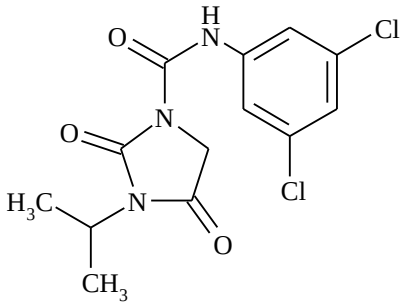
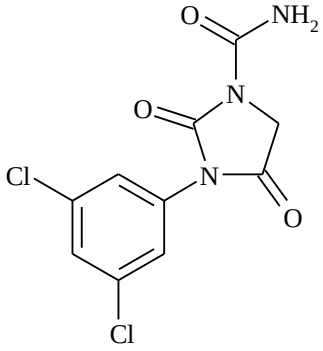
Compound	
Common name	Iprodione
Company experimental name	CPD-20
IUPAC name	3-(3,5-dichlorophenyl)-*N*-isopropyl-2,4-dioxoimidazolidine-1-carboxamide
CAS name	3-(3,5-dichlorophenyl)-*N*-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide
CAS registry number	36734-19-7
End-use products (EP)	Enclosure™ Flowable Fungicide and Nematicide (4.0 lb/gal FlC)
Chemical structure of isomer; RP-30228; isoiprodione	 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide
Chemical structure of metabolite; RP-32490; iprodione amide	 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine-carboxamide

Table A1.2. Physicochemical Properties of the Technical Grade of Iprodione.		
Parameter	Value	Reference
Melting point	~128 °C	Product Chemistry Chapter to Iprodione RED (DP# 234629, 3/26/97, J. Abbotts)
pH	Not applicable since the T/TGAI is not dispersible in water	
Density	1.0 g/mL at 20 °C	DP# 233155, 2/19/97, J. Abbotts
Water solubility	Iprodione is practically insoluble in water (13 mg/L).	Product Chemistry Chapter to Iprodione RED (DP# 234629, 3/26/97, J. Abbotts)
Solvent solubility	Iprodione is soluble in dichloromethane (45 g/100 mL), acetone (34 g/100 mL), ethyl acetate (23 g/100 mL), acetonitrile (17 g/100 mL), and toluene (15 g/100 mL)	
Vapor pressure	$<1 \times 10^{-7}$ mm Hg (25 °C)	DP# 233154, 2/19/97, J. Abbotts
Dissociation constant, pK_a	Not applicable since the T/TGAI is not dispersible in water	
Octanol/water partition coefficient, $Log(K_{OW})$	K_{OW} average of 974.7 at pH 3; K_{OW} average of 1006 at pH 5	DP# 189210, 6/4/93, F. Toghrol
UV/visible absorption spectrum	Not available	

Attachment 2. Toxicity Profile Tables

Table A2.1 Acute Toxicity Profile – Iprodione

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral [rat]	42306301	LD_{50} = 4468 mg/kg	III
870.1200	Acute dermal [rabbit]	40567601	LD_{50} > 2000 mg/kg	III
870.1300	Acute inhalation [rat]	42946101	LC_{50} > 5.16 mg/L	IV
870.2400	Acute eye irritation [rabbit]	41867301	Mild irritant	III
870.2500	Acute dermal irritation [rabbit]	41867302	Not an irritant	IV
870.2600	Skin sensitization [guinea pig]	40567602 42524601	Not a dermal sensitizer	-

Table A2.2 Subchronic, Chronic and Other Toxicity Profile – Iprodione

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100	90-Day oral toxicity (rat) TXR No.010747	42960701 (1993) 0, 1000, 2000, 3000, or 5000 ppm (diet) Acceptable/non-guideline Males: 0, 78, 151, 252, or 355 mg/kg/day Females: 0, 89, 189, 266, or 408 mg/kg/day	NOAEL = 1000 ppm (males 78/females 89 mg/kg/day LOAEL = 2000 ppm (males 151/females 189 mg/kg/day), based on decreased body weight/gain, decreased food consumption/food utilization, organ weight effects (decreased ovary weight) and microscopic lesions in the sex organs (testicular interstitial cell hyperplasia, uterine atrophy, decreased number of corpora lutea) and adrenals (enlargement of cells of zona glomerulosa, fine vacuolation of zona fasciculate). At HDT, decreased absolute brain, decreased relative ovary, uterus, pituitary, and adrenal weights
870.3100	90-Day oral toxicity (mouse)	48125502 (1989) 0, 1500, 3000, 6000, or 12000 ppm (diet) Acceptable/non-guideline Males: 0, 260, 509, 1066, or 2130 mg/kg/day Females: 0, 327, 659, 1303, or 2608 mg/kg/day	NOAEL – 1500 ppm, 260/327 mg/kg/day LOAEL = 3000 ppm, 509/659 mg/kg/day, increased adrenal weight, and microscopic adrenal findings

Table A2.2 Subchronic, Chronic and Other Toxicity Profile – Iprodione			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3150	90-Day oral toxicity (dog)	MRID 00157377 (1976) MRID 00157378 (1977) MRID 00232702 (1976) Unacceptable; 2 dogs/sex 0, 800, 2400, or 7200 ppm 0, ≈ 60, 180, 270 mg/kg/day (0.075 conversion)	NOAEL = 2400 ppm (≈180 mg/kg/day). LOAEL = 7200 ppm (≈270 mg/kg/day), based on liver hypertrophy and increased alkaline phosphatase.
870.3200	21-Day dermal toxicity (rabbit)	42023201(1991) 424468401 (1992) Acceptable/guideline 0, 100, 500, or 1000 mg/kg/day (21 days)	NOAEL = 1000 mg/kg/day LOAEL =no deaths, clinical signs of toxicity, no adverse effects on BW, FC, the skin, liver, or kidneys.
870.3465	90-Day inhalation toxicity (species)	Not available	Waived by HASPOC; TXR#0056453, 10/16/12
870.3700a	Prenatal developmental in Sprague-Dawley rats Sex differentiation study TXR No. 012400	44365001 (1997) Acceptable/non-guideline 0, 20, 120, or 250 mg/kg/day GD 6-19	**Maternal** NOAEL = 20 mg/kg/day. LOAEL = 120 mg/kg/day, based on decreased BWG and decreased food efficiency. 7 dams had enlarged adrenals (bilateral). At 250 mg/kg/day, there were 9 out of 25 deaths and 20 dams had enlarged adrenals. **Developmental** NOAEL = 20 mg/kg/day LOAEL = 120 mg/kg/day based on decreased anogenital distance (AGD) in the male pups.
870.3700a	Prenatal developmental in Crl:CD®BR/VAF/PLUS rats TXR No. 006359 TXR No. 007008	MRID 00162983 (1986) MRID 00162984 (1986) MRID 40514901 (1987) MRID 40514909 (11987) Acceptable/guideline 0, 40, 90, or 2000 mg/kg/day GD 6-15	**Maternal** NOAEL = 200 mg/kg/day (maternal toxicity not observed) LOAEL = **Developmental** NOAEL = 90 mg/kg/day LOAEL = 200 mg/kg/day based on delayed fetal developmental (slightly reduced fetal body weight and increased incidences of space between the body wall and organs in the fetuses.

Table A2.2 Subchronic, Chronic and Other Toxicity Profile – Iprodione			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700a	Prenatal developmental in (Sprague-Dawley rat)	0071324 (1976) Unacceptable/non-guideline does not appear to provide a robust evaluation of fetal effects following *in utero* exposure 0, 100, 200, or 400 mg/kg/day GD 5-15	**Maternal** NOAEL = 200 mg/kg/day LOAEL = 400 mg/kg/day based on slightly decreased BWG and significantly decreased food consumption. **Developmental** NOAEL = 200 mg/kg/day LOAEL = 400 mg/kg/day based on decreased implantation sites.
870.3700b	Prenatal developmental in (New Zealand rabbit) TXR No. 005214	MRID 00155469 (1985) Acceptable/guideline 0, 20, 60, or 200 mg/kg/day GD6-18	**Maternal** NOAEL = 20 mg/kg/day LOAEL = 60 mg/kg/day based on decreased body weight gain. At 200 mg/kg/day, there was an increased rate of abortions (7 does; GD 17-23), body weight loss, decreased food consumption, decreased defecation and urination in females that aborted. **Developmental** NOAEL = 60 mg/kg/day LOAEL = 200 mg/kg/day based on abortions, and increased incidence of skeletal variations (13^{th} full rib, malaligned sternebrae, and/or 27 presacral vertebrae, with or without delayed ossification.
870.3800	Reproduction and fertility effects (rat) TXR No.009695	MRID 00162983 (1986) MRID 41871601 (1991) acceptable/guideline* 0, 300, 1000, or 3000/2000 ppm males: 0, 18.5, 61.4, 154.8 mg/kg/day females: 0, 22.5, 76.2, or 201.2 mg/kg/day *sperm parameters not assessed; new 870.3800 required (1998)	**Parental/Systemic** NOAEL = 300 ppm, 18.5/22.5 mg/kg/day LOAEL = 1000 ppm, 61.4/76.2 mg/kg/day based on decreased body weight, body weight gain, and food consumption in both sexes. At the highest dose tested, increase in number of pups found dead, cannibalized or missing (F1a phase); 1 control and 11 high-dose dams sacrificed (LD 1-25) following death of entire litter. **Reproductive** NOAEL = 3000/2000 (155/201 mg/kg/day (HDT) **Offspring** NOAEL = 1000 ppm, 61/76 mg/kg/day LOAEL = 2000/3000 ppm, 155/201 mg/kg/day based on decreased pup viability and pup body weight, increased incidence of clinical signs (smallness of size, reduced mobility, unkempt appearance, hunching, or tremors) in pups during lactation period.

Table A2.2 Subchronic, Chronic and Other Toxicity Profile – Iprodione			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4100a	Chronic toxicity (Sprague-Dawley rat) TXR No. 010570	MRID 42637801 (1992) MRID 42787001 (1993) 0, 150, 300, or 1600 ppm Acceptable/guideline Males: 0, 6.1, 12.4, or 69 mg/kg/day Females: 0, 8.4, 16.5, or 95 mg/kg/day	NOAEL = 6.1/8.4 mg/kg/day. LOAEL = 12.4/16.5 mg/kg/day, based on increases in generalized enlargement of the cells of the zona glomerulosa in males and females, in fine vacuolation of the zona fasciculata and in generalized fine vacuolation of the zone reticularis in males in the adrenal cortex, an increased incidence of interstitial cell hyperplasia, reduced spermatozoa in the epididymides, reduced secretion of the seminal vesicles, increased hemosiderosis in the spleen in females, and increased liver weight. Tumors: increased incidence of both unilateral and bilateral benign interstitial cell tumors in the testes of males at the 1600 ppm dose level.
870.4100a	Chronic toxicity (Charles River CD rat)	MRID 00071997 (1978) MRID 00164249 (1978) MRID 00128931 (1983) Unacceptable 0, 125, 250, or 1000 ppm 0, 6.25, 12.5, or 50 mg/kg/day	NOAEL = 50 mg/kg/day. LOAEL = not identified. Incidence of testicular interstitial cell tumors was 2, 2, 4, 5 out of 60 rats/group.
870.4100b	Chronic toxicity (dog)	MRID 42211101 (1991) 0, 200, 300, 400, or 600 ppm Acceptable/non-guideline Males: 0, 7.8, 12.4, 17.5, or 24.6 mg/kg/day Females: 9, 9.1, 13.1, 18.4, or 26.4 mg/kg/day	NOAEL = 17.5/18.4 mg/kg/day LOAEL = 24.6/26.4 mg/kg/day, based on a decrease in red blood cell (RBC, HGB, HCT) values.
870.4100b	Chronic toxicity (dog) TXR No. 005882	MRID 00144391 (1984) MRID 41327001 (1989) Acceptable/guideline 0, 100, 600, 3600 ppm Males: 0, 4.1, 24.9, or145.3 mg/kg/day Females: 0, 4.3, 28.3, or 152.5 mg/kg/day	NOAEL = 4.1/4.3 mg/kg/day LOAEL = 24.9/28.3 mg/kg/day, based on decreased prostate weight and an increased incidence of erythrocytes with Heinz bodies.

Table A2.2 Subchronic, Chronic and Other Toxicity Profile – Iprodione			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4200	Carcinogenicity (rat) TXR No. 010570	MRID 42637801 (1992) MRID 42787001 (1993) 0, 150, 300, or 1600 ppm Acceptable/guideline Males: 0, 6.1, 12.4, or 69 mg/kg/day Females: 0, 8.4, 16.5, or 95 mg/kg/day	NOAEL = 6.1/8.4 mg/kg/day. LOAEL = 12.4/16.5 mg/kg/day, based on increases in generalized enlargement of the cells of the zona glomerulosa in males and females, in fine vacuolation of the zona fasciculata and in generalized fine vacuolation of the zone reticularis in males in the adrenal cortex, an increased incidence of interstitial cell hyperplasia, reduced spermatozoa in the epididymides, reduced secretion of the seminal vesicles, increased hemosiderosis in the spleen in females, and increased liver weight. At HDT, atrophy of seminiferous tubules in testes, with atrophy of prostate and absence of spermatozoa in epididymides; increased incidence of tubular hyperplasia in ovaries and increased sciatic nerve fiber degeneration in females **evidence of carcinogenicity:** increased incidence of both unilateral and bilateral benign interstitial cell tumors in the testes at the 1600 ppm.
870.4300	Carcinogenicity (mouse) TXR No. ?	MRID 42825002 (1993) 0, 160, 800, or 4000 ppm Acceptable/guideline Males: 0, 23, 115, or 604 mg/kg/day Females: 0, 27, 138, 793 mg/kg/day	NOAEL = 23/27 mg/kg/day LOAEL = 115/138 mg/kg/day, based on the increased incidence of centrilobular hepatocyte enlargement in females and the increased incidence of generalized vacuolation/ hypertrophy of the interstitial cells in the testes of males. At the highest dose tested, increase in the incidence of benign ovarian tumors [luteoma] in females compared to the control incidence, which was accompanied by an increase in luteinization of the interstitial cells, corpora lutea absent, and prominent granulosa cells. **evidence of carcinogenicity:** increased incidence of hepatocellular tumors in both sexes
870.4300	Carcinogenicity (mouse)	MRID 00070963 (1978) Unacceptable 0, 200, 500, or 1250 ppm 0, 30, 75, or 187.5 mg/kg/day	NOAEL = 187.5 mg/kg/day LOAEL = not identified. **No evidence of carcinogenicity**

Table A2.2 Subchronic, Chronic and Other Toxicity Profile – Iprodione			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Gene Mutation 870.5100	Salmonella typhimurium TA98, TA100, TA1535, Ta1537, Ta1538	41604106 (1990) Acceptable/guideline	Negative with and without metabolic activation; reductions in mean numbers of revertants and background lawn at highest dose –S9; precipitate at dose ≥250 µg/plate ±S9
Mammalian cell forward gene mutation assay 870.5300	*CHO/HGPRT*	00148206 (1985) Acceptable/guideline	Did not induce mutation with or without metabolic activation.
In vitro chromosomal aberration assay 870.5375	Chinese hamster ovary (CHO) cells (+/-S9)	00148207 (1985) Acceptable/guideline 0, 40, 150, 400 µg/mL +S9 0, 15, 75, 150 µg/mL –S9	Negative +/-S9; precipitation at ≥150 µg/mL
In vivo mouse micronucleus assay 870.5395	CD-1 mouse	43535001 (1994) Acceptable/guideline 0, 750, 1500, or 3000 mg/kg (one dose)	No evidence of a clastogenic or aneugenic effect at any dose level or harvest time.
Other Effects 870.5500	DNA damage in Bacillus subtilis	MRID 00148208 (1985) Acceptable/guideline	Positive with and without metabolic activation
Other Effects 870.5900 sister chromatid exchange assay	Chinese hamster ovary cells	00148209 (1985) Acceptable/guideline	Negative both with and without metabolic activation
870.6200a	Acute neurotoxicity screening battery	Not available	Waived by HASPOC; TXR#0056453, 10/16/12
870.6200b	Subchronic neurotoxicity screening battery	Not available	Waived by HASPOC; TXR#0056453, 10/16/12
870.6300	Developmental neurotoxicity	Not available	Conditionally required
870.7485	Metabolism and pharmacokinetics (species)	MRID 42984101 MRID 41346701 MRID 43484901 (1994)	

Table A2.2 Subchronic, Chronic and Other Toxicity Profile – Iprodione			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
	Levels of iprodione in testes and plasma TXR No. 013804	MRID 44750701 () Acceptable/non-guideline	Iprodione and metabolites reach target organ (testes)
870.7600	Dermal penetration (rat, male) (TXR No. 011645)	MRID 43535003 (1994) Acceptable/guideline Single dose: 0.4, 4.0, 40 mg/rat for 0.5, 1, 2, 4, 10, or 24 hours	Skin residues increased with duration of exposure to 5-10% of applied dose; absorption appears saturated at 4 and 40 mg/rat; following a 10-hour exposure, ≈5% is absorbed; following 24-hour exposure, ≈15% is absorbed.
870.7800	Immunotoxicity Sprague-Dawley female rat	MRID 48649101 (2010) Acceptable/Guideline	No evidence of immunotoxicity was observed in female Sprague-Dawley rats at 225 mg/kg/day, the highest dose tested.
	Pubertal toxicity study (Sprague-Dawley male rat)	MRID 48279201 (2007) Toxicology Letters 174: 74-81, 2007.	NOAEL = not identified for testosterone effect. LOAEL = 50 mg/kg/day, based on significant, dose-related *reductions in serum testosterone levels (↓73%)*. NOAEL = 50 mg/kg/day LOAEL = 100 mg/kg/day, based on a delay in preputial separation (PPS)
	Special mechanistic study Immature pocine cultured Leydig cells	MRID 44171901 (1996) Acceptable/non-guideline *In vitro*	Iprodione and its metabolites (RP36115 and RP36112) appear to modulate Leydig cell steroidogenesis by interfering at the level of cholesterol transport and/or steroidogenic enzyme activity.
	Special mechanistic study Male CD® Sprague-Dawley rats TXR No. 012192	MRID 44171903 (1996) Acceptable/non-guideline *In vitro* Endocrine Challenge Test (ECT) using human chorionic gonadotropin (hCG) *In vivo* (prior exposure *via* diet for 14 days at 3000 ppm) Testicular sections incubated with 0, 1, 10, or 100 µg/mL iprodione for 1 hour	Dose-related reduction in testosterone secretion from testicular sections incubated *in vitro* with iprodione, with and without hCG stimulation; prior exposure of rats *in vivo* for 14 days appeared to have little effect on secretion of testosterone, with and without hCG stimulation from testicular sections incubated *in vitro* other than a slight increase initially.

Table A2.2 Subchronic, Chronic and Other Toxicity Profile – Iprodione			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
	Special mechanistic study Sprague-Dawley male rat TXR No. 012192	44171904 (1996) Acceptable/non-guideline Human chorionic gonadotropin (hCG) Endocrine Challenge Test (ECT) *In vivo* diet exposure for 2, 7, or 14 days at 3000 ppm	Iprodione did not produce alterations in testicular function following dietary exposure at 3000 ppm for 14 days.
	Special mechanistic study Male rat TXR No. 011645	MRID 43535002 (1994) MRID 44203401 (1996) Acceptable/non-guideline	Iprodione has poor binding affinity to androgen receptor following exposure; Marked increase in adrenal weights was accompanied by histopathological lesion (vacuolation) indicative of an alteration of steroidogenesis following 30 day exposure.
	Special mechanistic study Male rat	MRID 44729201 (1998) Acceptable/non-guideline 0, 70, 300 mg/kg (gavage) Single dose	Decreased testosterone concentration at 2hours (↓59%** @ 70/↓75%** @ 300 mg/kg) and at 4 hours (↓29% @ 70/↓59%* @ 300 mg/kg); increased luteinizing hormone concentration at 2 hours (↑24% @ 70/↑33%* @ 300 mg/kg) and at 4 hours (↑36%* @ 70/↑55%** @ 300 mg/kg)
	Special mechanistic study Male rat	MRID 45859601 (2001) Acceptable/non-guideline 0, 70, 300 mg/kg (gavage) Single dose	Decreased testosterone concentration at 30 minutes (↓48%** @ 70/↓49%** @ 300 mg/kg), at 1 hour (↓49%** @ 70/↓67%** @ 300 mg/kg), at 2 hours (↓64%** @ 70/↓56%** @ 300 mg/kg), and at 4 hours (↓35% @ 70/↓54%** @ 300 mg/kg); increased luteinizing hormone concentration at 4 hours (↑10% @ 70/↑30%** @ 300 mg/kg)
	Special mechanistic study Male rat TXR No. 0052725	MRID 45859602 (2002) Acceptable/non-guideline 0, 6, 70, 300 mg/kg/day (gavage for 14 days)	Dose-related increase in mean BrdU labeling index at 70 (↑36%) and 300 (↑74%) mg/kg/day during 2nd week assessment. At 6 mg/kg/day there was a slight (↑10%) increase. Demonstrates an increase in Leydig cell proliferation in the testis.

Table A2.2 Subchronic, Chronic and Other Toxicity Profile – Iprodione			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
	Special mechanistic study Male rat TXR No. 0052725	MRID 45859603 (2002) Acceptable/non-guideline 0, 6, 70, 300 mg/kg/day (gavage for 14 days)	Decreased testosterone concentration at 1 hour (↓17% @ 6/26% @ 70/↓36%* @ 300 mg/kg), at 2 hour (↓9% @ 6/↓44%* @ 70/↓37%* at 300 mg/kg), at 4 hours (↓48%** @ 300 mg/kg), and recovery at 24 hours. Increased luteinizing hormone concentration at 2 hours (↑32% @ 70/↑39%** @ 300 mg/kg) and at 4 hours (↑24% @ 70/↑54% @ 300 mg/kg/day.
	Special mechanistic study Cultured Leydig cells TXR No.011907	MRID 43830601 (1995) Acceptable/non-guideline 1-10 µg/mL (3-hour exposure)	Inhibited gonadotrophin-stimulated testosterone secretion; not related to Leydig cell damage because removal of iprodione from culture medium resulted in recovery of cells' ability to secrete testosterone following hCG stimulation.
	Special mechanistic study CD-1 mouse (male)	MRID 44171902 (1996) Acceptable/non-guideline 3- and 14-day oral exposure 0, 4000 ppm (696 mg/kg/day) or 12000 ppm (2138 mg/kg/day)	Iprodione, at dose levels 5- and 15- fold greater than the LOEL for liver effects observed in the mouse carcinogenicity study, induces (1) liver cell proliferation, (2) increased microsomal enzyme activities, (3) an increase in total cytochrome P-450 content, and (4) centrilobular hypertrophy, which most closely resemble the pattern of liver effects observed following phenobarbital exposure.

Attachment 2. Iprodione and 3,-5-DCA Endpoints

Table A2.1. Summary of Toxicological Doses and Endpoints for Iprodione for Use in Dietary Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD/PAD	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	No acute endpoint was identified in the database. It is noted that a decline in testosterone for a short time period (repeat exposure) during puberty could potentially result in delayed puberty as well as other adverse effects, but a delay in puberty or other adverse outcomes would not be expected from an acute (single) exposure. A transient decline for a few hours in an adult or young animal would not likely cause any adverse, permanent effects.			
Acute Dietary (Females 13-49 years of age)	LOAEL = 50 mg/kg/day	UF_A 10x UF_H 10x FQPA:$UF_{LOAEL \rightarrow NOAEL}$ = 10x Total UF: 1000	aRfD = 0.05 mg/kg aPAD = 0.05 mg/kg	Male pubertal toxicity study (rat) MRID 48279201 LOAEL = 50 mg/kg/day, based on significant, dose-related *reductions in serum testosterone levels (↓73%)*; delay in PPS at 100 mg/kg/day Developmental toxicity study (rats) MRID 44365001 LOAEL = 120 mg/kg/day based on decreased AGD in male pups (single dose effect)
Chronic Dietary (All Populations)	LOAEL = 50 mg/kg/day	UF_A 10x UF_H 10x FQPA:$UF_{LOAEL \rightarrow NOAEL}$ = 10x Total UF: 1000	cRfD = 0.05 mg/kg/day cPAD = 0.05 mg/kg/day	Co-critical studies: Chronic oral toxicity (rat) and Male pubertal toxicity study (rat) Chronic Oral Toxicity: MRID 42637801/42787001 NOAEL = 6.1 mg/kg/day. LOAEL = 12.4 mg/kg/day, based on increases in generalized enlargement of the cells of the zona glomerulosa in males and females, in fine vacuolation of the zona fasciculata and in generalized fine vacuolation of the zone reticularis in males in the adrenal cortex, an increased incidence of interstitial cell hyperplasia, reduced spermatozoa in the epididymides, reduced secretion of the seminal vesicles, increased hemosiderosis in the spleen in females, and increased liver weight. Male pubertal toxicity (rat) MRID 48279201 LOAEL = 50 mg/kg/day, based on significant, dose-related *reductions in serum testosterone levels (↓73%)*

Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose.

Table A2.2. Summary of Toxicological Doses and Endpoints for Iprodione for Use in Non-Occupational Human Health Risk Assessments (Dermal and Inhalation)

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal and Inhalation (short- and intermediate-term)	LOAEL = 50 mg/kg/day	UF_A 10x UF_H 10x FQPA:$UF_{LOAEL\rightarrow LOAEL}$ = 10x Total UF: 1000	LOC for MOE < 1000	Co-critical studies: Chronic oral toxicity (rat) and Male pubertal toxicity study (rat) Chronic Oral Toxicity: MRID 42637801/42787001 NOAEL = 6.1 mg/kg/day. LOAEL = 12.4 mg/kg/day, based on increases in generalized enlargement of the cells of the zona glomerulosa in males and females, in fine vacuolation of the zona fasciculata and in generalized fine vacuolation of the zone reticularis in males in the adrenal cortex, an increased incidence of interstitial cell hyperplasia, reduced spermatozoa in the epididymides, reduced secretion of the seminal vesicles, increased hemosiderosis in the spleen in females, and increased liver weight. Male pubertal toxicity (rat) MRID 48279201 LOAEL = 50 mg/kg/day, based on significant, dose-related *reductions in serum testosterone levels*.

Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. FQPA SF = FQPA Safety Factor. LOC = Level of Concern.

Cancer Assessment

Iprodione has been classified as a "Likely" human carcinogen, based on the increased incidence of liver tumors in both sexes of the mouse and the increased incidence of Leydig cell tumors in male rats. The registrant previously submitted mode of action (MOA) data; however, the Cancer Assessment Review Committee (CARC) determined that the MOA data do not provide a sufficient basis for establishing an MOA for iprodione for either tumor type. Therefore the Agency has determined that it is appropriate to quantify cancer dose response using the linearized low dose extrapolation model (Q_1* approach), and the Leydig cell tumor Q_1* of 4.39×10^{-2} was chosen for human health risk assessment as the most sensitive endpoint.

The only concern identified for 3,5-DCA is a potential carcinogenicity concern. A surrogate Q_1* was used to obtain the carcinogenic risk estimate for 3,5-DCA. Since 3,5-DCA is not a registered pesticide; there are no toxicology data for this compound. Consequently, the established Q_1* of 6.38×10^{-2} $(mg/kg/day)^{-1}$ for p-chloroaniline (PCA) was used in this assessment because of the structural similarities between 3,5-DCA and PCA. HED believes that the use of the PCA Q_1* represents a reasonable upper bound risk estimate.

Attachment 3. Iprodione International Residue Limits Table

Table A3. Summary of US and International Tolerances and Maximum Residue Limits for Iprodione

Residue Definition:	
US	40 CFR 180.399: Plant: combined residues of the fungicide iprodione [3-(3,5-dichlorophenyl)- N -(1-ethylethyl)-2,4-dioxo-1-imidazolidinecarboxamide], its isomer 3-(1-methylethyl)- N -(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide, and its metabolite 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine-carboxamide Livestock: combined residues of iprodione [3-(3,5-dichlorophenyl)- N -(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide], its isomer [3-(1-methylethyl)- N -(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide, and its metabolites [3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine-carboxamide] and [N -(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide], all expressed as iprodione equivalents
Canada	Plant: 3-(3,5-dichlorophenyl)-N-isopropyl-2-4-dioxoimidazolidine-1-carboxamide, including the metabolites 3-isopropyl-N-(3,5-dichlorophenyl)-2,4-dioxoimidazolidine-1-carboxamide and 3-(3,5-dichlorophenyl)-2,4-dioxoimidazolidine-1-carboxamide
Mexico[1]	
Codex[2]	Plant: Iprodione

Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex[2]
Plant Commodities with U.S. Tolerances				
Almond, hulls	2.0			
Almond	0.3			0.2
Apricot	20.0	3.0		
Bean, dry, seed	2.0	0.3 beans		0.1 beans (dry)
Bean, forage	90.0			
Bean, succulent	2.0			2 common bean (pods and/or immature seeds)
Blueberry	15.0			
Boysenberry	15.0			
Broccoli	25.0			25
Caneberry subgroup 13A	25.0	10 raspberries		30 blackberries, raspberries, red, black
Carrot, roots	5.0	5.0		10 Po
Cherry, sweet, postharvest	20.0	5.0 cherries		10 cherries
Cherry, tart	20.0			
Cotton, undelinted seed	0.10			
Cowpea, hay	90.0			
Currant	15.0			
Garlic	0.1			
Ginseng	2.0			
Ginseng, dried root	4.0			
Grape	60.0	10		10
Grape, raisin	300	60 raisins		
Kiwifruit	10.0	0.5 (edible portion)		5

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Lettuce	25.0	15		10 lettuce, head 25 lettuce leaf
Nectarine, postharvest	20.0	10 peaches/nectarines		
Onion, bulb	0.5			0.2
Peach, postharvest	20.0	10 peaches/nectarines		10 peach
Peanut	0.5			
Peanut, hay	150.0			
Plum, postharvest	20.0	2.0 plums		
Plum, prune	20.0	2.0 prunes		
Potato	0.5			
Raspberry	15.0	10 raspberries		
Rice, bran	30.0			
Rice, grain	10.0			10 rice husked
Rice, hulls	50.0			
Rice, straw	20.0			
Strawberry	15.0	5.0		10
Plant Commodities with International MRLs and NO US Tolerance				
Barley				2
Common bean (pods and/or immature seeds)				2
Cucumber		0.5		2
Leeks		13		
Pome fruits				5 Po
Rapeseed (canola)		1.0		0.5
Sugar beet				0.1 (*)
Sunflower seed				0.5
Tomatoes		0.5		5
Witloof chicory (sprouts)				1
Wine		5.0		
Livestock Commodities				
Cattle, fat	0.5			
Cattle, kidney	3.0			
Cattle, liver	3.0			
Cattle, meat	0.5			
Cattle, meat byproducts, except kidney and liver	0.5			
Egg	1.5			
Goat, fat	0.5			
Goat, kidney	3.0			
Goat, liver	3.0			
Goat, meat	0.5			
Goat, meat byproducts, except kidney and liver	0.5			
Hog, fat	0.5			
Hog, kidney	3.0			
Hog, liver	3.0			
Hog, meat	0.5			
Hog, meat byproducts, except kidney and liver	0.5			
Horse, fat	0.5			
Horse, kidney	3.0			
Horse, liver	3.0			

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Horse, meat	0.5			
Horse, meat byproducts, except kidney and liver	0.5			
Milk	0.5			
Poultry, fat				
Poultry, liver	5.0			
Poultry, meat	1.0			
Poultry, meat byproducts, except liver	1.0			
Sheep, fat	0.5			
Sheep, kidney	3.0			
Sheep, liver	3.0			
Sheep, meat	0.5			
Sheep, meat byproducts, except kidney and liver	0.5			
Completed: M. Negussie; 08/21/2012				

[1] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

[2] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.